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CARLSON, EXAMINER

18N2/0616

ELIZABETH A. HANLEY
LAHIVE & COCKFIELD
60 STATE STREET
BOSTON, MA 02109

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1812	16

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 3-18-94 #15 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1, 26-31, 33, 36, 37, 39, 40, 44-46, 50-138 are pending in the application.
   Of the above, claims 69-98, 101-138 are withdrawn from consideration.
2. ☒ Claims 2-25, 32, 34, 35, 38, 41, 43, 47-49 have been cancelled.
3. ☒ Claims 39, 56, 66 are allowed.
4. ☒ Claims 1, 26-31, 33, 36, 37, 40, 44-46, 50-55, 57-65, 67, 68, 99, 100 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

This Office Action is in response to Paper #15, filed March 18, 1994. Claims 2-25, 32, 34, 35, 38, 41, 43, and 47-49 have been cancelled. Claims 69-98 and 101-138 have been withdrawn from consideration by the Examiner as these Claims are drawn to non-elected inventions. Claims 1, 26-31, 33, 36, 37, 39, 40, 44-46, 50-68, 99 and 100 are currently under examination.

Applicant's election of Invention I in Paper No. 15 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)).

Because the amendments to the Claims have effectively changed the invention previously examined, the Examiner has chosen to first begin this Office Action with new rejections based on these amendments and then address the Applicants remarks concerning the rejections made in the previous Office Action.

New Rejections

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed. The specification does not teach how to make or use any DNA that is stabilized against cellular recombination. Recombination is the independent assortment of new combinations of genes in progeny that did not occur in the parents. Recombination, which is limited to DNA, should not be confused with protein expression (proteins do not recombine; neither do

cells). In terms of recombinant DNA technology, such terms as recombination implies stable transformation of a cell because the DNA or vector would have to be integrated into the host DNA to recombine. Additionally, plasmids may also recombine independent of chromosomal DNA. Therein, the specification does not teach how to make (and subsequently use) a DNA that is stabilized against recombination, that is, the technician-independent, cellular-dependent transition between transient and stable transformation of a cell or independent recombination between plasmids is prevented.

Claims 1, 28-31, 33, 40, 54, 55-68, 99, and 100 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1, 28-31, 33, 40, 54, 55-68, 99, and 100 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "cellular recombination" is not an art recognized term and does not appear to be defined in the specification. Therein, this term has no known meaning and renders the claimed Invention indefinite.

Because there is no prior art teaching how to stabilize DNA encoding CFTR such that this DNA cannot recombine, all art rejections previously applied to independent Claims 1 and 36 and Claims that exclusively depend from them (that is, not Claim 55 or 62, for example), is withdrawn.

Maintenance of objections and rejections:

The disclosure is objected to because of the following informalities: mistypes throughout the specification and claims.

This same rejection has been made in Papers #2 and #12 and no attempts have been made to make any corrections. Further, though the specification defines intron and intervening sequences to be the same, Claim 27 should be amended to recite "intron" for consistency with Claim 26 from which it depends. Appropriate correction is required.

Applicants have not addressed this issue.

Claims 50-53 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the DNA encoding the CFTR protein of Fig. 1 as discussed in the previous Office Action. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Claim 50 is for any DNA comprising the synthetic "intron" in Fig. 6. The Claims should be limited to only that DNA encoding the CFTR or the synthetic intron of the instant invention and not other CFTR known or unknown. It would require undue experimentation to determine DNA having such an intron and if that intron would render the host expression of the DNA silent because it is not predictable if the intron depicted in Fig. 6 is an exon in other proteins, such as observed in splicing.

Applicants have not argued the rejection of Claims 50-54.

Claims 36, 37, 46, 55-57, and 62-64 are rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Collins et al. (USP 5,240,846).

Collins et al. teach vectors for the expression of the CFTR gene to be used for gene therapy. Collins et al. deliver and express a single normal copy of the CFTR gene and this corrects the chloride regulatory defect in human colon tumor cell lines. The transfer of the gene is by fusing the target cell to liposomes (col. 3, 15), plasmids, viral vectors, and retroviruses (col. 3). Collins et al. teach to place the DNA encoding CFTR into low copy

vectors to prevent cell death during expression of CFTR (col. 2). The cDNA taught by Collins et al. is 99% identical to that disclosed by the Applicants in Table 1. The base difference at position 1990 may be incidental and changes the amino acid at position 620, over 100 amino acids from the active region of CFTR at position 508, from His to Asn. Therein, the DNA encoding the CFTR of Collins et al. anticipates the claimed Invention. Alternatively, it would have been obvious to a person of ordinary skill in the art that the DNA encoding CFTR as disclosed in Table 1 can be used to treat CF because Collins et al. teach that a DNA 99% identical to this DNA is useful for treating CF. Therein, these Claims remain anticipated by Collins et al. or alternatively as obvious over Collins et al.

Applicants argue that the DNA of Table 1 is not taught by Collins. As noted in the previous Office Action, these DNAs are nearly identical and changing Claim 36 to read that the CFTR is encoded by that DNA described in Table 1 does not prevent the DNA from being anticipated or rendered obvious over the teachings of Riordan et al.
Collins

Claims 26, 55-57, and 62-64 are rejected under 35 U.S.C. § 102(a) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Riordan et al.

Riordan et al. cloned the CFTR gene from epithelial cells to determine the role of Phe508 in CF. Most of the cDNA isolated contained sequence insertions corresponding to introns (page 1067, col. 1). The cDNA taught by Riordan et al is 99% identical to that disclosed by the Applicants in Table 1. The base difference at position 1990 may be incidental and changes the amino acid at position 620, over 100 amino acids from the active region of CFTR at position 508, from His to Asn. Therein, the DNA encoding the CFTR of Riordan et al. anticipates the claimed Invention. Alternatively, it would have been obvious to a person of ordinary skill in the art that the DNA encoding CFTR as disclosed in Table 1 can be used to study the role of Phe508 in CF because

Riordan et al. teach that a DNA 99% identical to this DNA is useful for studying the actions of Phe508 CFTR. Therein, these Claims remain anticipated by Riordan et al. or alternatively as obvious over Riordan et al.

Applicants argue that the DNA of Table 1 is not taught by Riordan et al. As noted in the previous Office Action, these DNAs are nearly identical and changing Claim 26 to read that the CFTR is encoded by that described in Table 1 does not prevent the DNA from being anticipated or rendered obvious over the teachings of Riordan et al.

Claims 44, 45, 58, 60, 61, 65, 67, and 68 are rejected under 35 U.S.C. § 103 as being unpatentable over Collins et al (USP 5,240,846) as discussed in the previous Office Action.

Applicants explain how the cancellation of and amendments to Claims effect this rejection. However, Applicants provide no basis for the statement that the teachings of Collins et al. do not render the instant Invention obvious. Therein, this rejection is maintained.

Claims 58, 60, 61, 65, 67, and 68 are rejected under 35 U.S.C. § 103 as being unpatentable over Riordan et al. (1989) as discussed in the previous Office Action.

Applicants explain how the cancellation of and amendments to Claims effect this rejection. However, Applicants provide no basis for the statement that the teachings of Riordan et al. do not render the instant Invention obvious. Therein, this rejection is maintained.

Claims 99, and 100 are rejected under 35 U.S.C. § 103 as being unpatentable over Riordan et al. as applied to claims 60, 61, 65, 67, and 68 above, and further in view of Sambrook et al. (1989) as discussed in the previous Office Action.

Applicants explain how the cancellation of and amendments to Claims effect this rejection. However, Applicants provide no basis for the statement that the teachings of Riordan et al. in view of Sambrook et al. do not render the instant Invention obvious. Therein, this rejection is maintained.

Claims 39, 59, and 66 are free of the prior art of record. The plasmid of Claim 39 encoding both the CFTR and the intron of Fig. 6 in a low copy vector for the production of DNA in E. coli without subsequent destruction of the host cells appears to be novel over the prior art of record. Claims 59 and 66 are directed to alternative cell lines for the expression of CFTR. Such expression is briefly described on page 20 of the specification. Neither Collins et al. or Riordan et al. suggest that insect cells, fungi, or plant cells can be used to express CFTR and it is not obvious that one of ordinary skill in the art would want to express CFTR in these cell lines.

The Examiner believes that all pertinent arguments have been addressed.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication should be directed to Karen Cochrane Carlson, Ph.D. at telephone number (703) 308-0034.
Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GARNETTE D. DRAPER
SUPERVISORY PATENT EXAMINER
GROUP 1800